DOI:10.31557/APJCC.2023.8.3.491

RESEARCH ARTICLE

Evaluation of Response and Toxicity in Patients with Locally Advanced Rectal Cancer Treated with Neoadjuvant Chemoradiation

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Abstract

Purpose: To study the response after neoadjuvant chemoradiation in patients with locally advanced rectal cancer with capecitabine 825 mg/m^2 daily PO bid with radiation at a dose of 45Gy/20#/4 weeks, to study the clinical profile of different patients with locally advanced rectal cancer, and to assess the toxicity of patients treated with neoadjuvant chemoradiationtherapy. **Materials and Methods:** A prospective observational study was conducted in 60 patients with histopathologically proven locally advanced rectal carcinoma from October 2018 to April 2020 . Neoadjuvant chemoradiation was planned with capecitabine 825 mg/m^2 PO bid with radiation at a dose of 45 Gy/20#/4 weeks. Radiological response was assessed 6 weeks after treatment completion, and surgery was planned according to the response. **Results:** Thirty-seven patients underwent definitive surgery. Pathological complete response was observed in one patient, near complete response in seven, partial response in 27, and poor or no response in two patients. Of 37 patients who have undergone surgery, 30% of patients received sphincter preserving surgery. Radiation-induced acute skin and lower gastrointestinal tract lesions were observed. Capecitabine-induced diarrhea, hematological toxicities, and a few patients with hand foot syndrome were observed. **Conclusion:** In locally advanced rectal cancer, preoperative radio-chemotherapy with capecitabine improves local control and reduces the risks of acute and late toxicity compared to postoperative radiochemotherapy. Thus, preoperative radiochemotherapy with capecitabine is safe and well tolerated in locally advanced rectal cancer, especially in tumors of the lower and middle rectum.

Keywords: Rectal Cancer- Capecitabine- Neoadjuvant Chemoradiation

Asian Pac J Cancer Care, **8 (3)**, 491-496

Submission Date: 01/12/2023 Acceptance Date: 04/27/2023

Introduction

Rectal cancer, also known as colorectal or bowel cancer, is the second most common cancer in the large intestine and is one of the major public health problems. Its prevalence is higher in developed regions of the world than in developing countries [1]. It is third most common cancer in men and second in women in world [2]. According to recent data (Globocan 2020) in India new cases of colorectal cancer account for 65358 (4.9%) cases. Out Of these males corresponds to 40408 (6.3%) and female to 24950 (3.7%) cases. The 5-year prevalence of all ages include approximately 62827 cases [3].

Different types of treatment modalities have been proposed for patients with rectal cancer. Preoperative chemoradiation has become a part of the treatment protocols for stage II and III rectal cancer. Compared to postoperative chemoradiotherapy, the advantages of preoperative chemoradiation are improved compliance, reduced toxicity, and tumor downstaging in a substantial number of patients. It also enhances the rate of curative surgery, permits sphincter preservation in patients with low-sited tumors, and has a positive impact on the quality of life [4]. Orally administered capecitabine mimics the pharmacokinetics of continuous 5-FU infusion and makes chemoradiotherapy patient-friendly. The mechanism of capecitabine activation, preferably in tumor cells, may further enhance its efficacy and tolerability, offering the

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potential for an enhanced therapeutic ratio [5-7].

Surgery is the primary treatment modality for rectal cancer, but in patients with invasion through the rectal wall or positive lymph nodes, the major problem is local recurrence after surgery [8]. In case of localization in the lower third of the rectum, the surgical approach is more aggressive and destructive, with loss of sphincter function. Surgical technique can also influence the local recurrence rate. In fact, after an appropriate total mesorectal excision, local recurrence rates vary from 4 to 8 % [9-12]. The addition of a neoadjuvant therapeutic approach, particularly in patients with low rectal cancer, makes it possible to obtain a high rate of sphincter function preservation by using conservative surgery with effective results [13]. It also has lower toxicity than postoperative radiochemotherapy [14].The Purpose of this research study is to evaluate the response and toxicity in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation"

Aims and Objectives

Primary:

● To study the response after administering neoadjuvant chemoradiation in patients with locally advanced rectal cancer with capecitabine (825mg/m^2 daily PO bid) with radiation at a dose of 45 Gy/20 #/4 weeks.

Secondary:

● To study the clinical profile of different patients with locally advanced rectal cancer.

● To assess the toxicity of patients treated with neoadjuvant chemoradiation.

Materials and Methods

The study was conducted on patients with locally advanced rectal cancer who visited the Government Medical College and Cancer Hospital, Aurangabad, from October 2018 to December 2020.

Methods Of Collections Of Data:

Sample Size: Total 60 patients were recruited

Study design: Prospective, Observational study

Inclusion criteria

1. Patients with histologically proven diagnosis of locally advanced rectal adenocarcinoma clinical stage T2N+, T3 or T4, N0 or N1-N2, M0 suitable for pre-operative combined chemoradiotherapy

2. Ability and willingness to provide informed consent prior to participation in the study.

3. Eastern Cooperative Oncology Group (ECOG) performed status of 0-2

4. Adequate organ and bone marrow function based upon the following laboratory criteria

a) Hb>9gm/dl

b) Absolute neutrophil count >1500 /microliter

c) Platelet count >1 lakh

d) Creatinine <1.5 x ULN

e) ALT and AST <2.5 ULN

f) T. BILIRUBIN <1.5 ULN

Exclusion criteria

1. Previous RT on the pelvic region or previous CT

2. Patient with metastatic rectal cancer

3. Patients with serious illness or medical illness including significant cardiac disease

4. History of significant neurological or psychiatric disorders

5. Serious uncontrolled active infection

6. Pregnant or lactating women and women with child bearing potential unless using a reliable contraceptive method.

Baseline Screening Process and Recording

● History of patients, including complaints, medical illness, drug history, personal history, past medical history, and surgical history

● Clinical examination: general and systemic examination

● Hemogram, LFT, KFT, RBS, HIV, and HBsAg

● S.CEA

● CT Abdomen and pelvis

● Chest X-ray

● Sigmoidoscopy/Colonoscopy

● Biopsy

Sampling technique

Convenient sampling, the patients who were available during the duty of the investigator and met the selection criteria were included in the study as a sample.

Procedure

All cases of locally advanced rectal cancer were registered, and a detailed clinical history was obtained from all patients through thorough clinical examination.

They were further investigated with routine blood investigation and special investigation, and CEA and TNM staging were performed with CT of the abdominal pelvis before neoadjuvant chemoradiation and after 6 weeks of completion of neoadjuvant chemoradiation. Neoadjuvant chemoradiation was planned with capecitabine 825 mg/m^2 PO bid with radiation at a dose of 45 Gy/20#/4 weeks. Radiological response was assessed using Recist 1.1 criteria after 6 weeks of treatment completion. Those patients who met criteria for surgery undergone surgery either Abdominoperineal resection (APR) or Anterior Resection (AR).

Pathological response was assessed on the basis of post-operative histopathological report by Modified Ryan Scheme for Tumor Regression Score (Cap Guideline, College of American Pathologists).

Radiotherapy Details

Radiation was delivered with 6 or 10 MV photons using a 3-field technique (posterior and both laterals). Treatment planning was performed by computerized dosimetry, and a dose of 2.25Gy per fraction was prescribed to cover the planned target volume with (95% of the ICRU point dose). The patients were placed in the prone position. The patients were encouraged to have a full bladder during irradiation. Radiotherapy was administered 5 days per

week, once per day, at 2.25 Gy per day. The entire pelvis received 45 Gy/20 # over four weeks.

Target Volumes for Gross and Microscopic Disease in Neoadjuvant Setting

GTV: All gross disease on physical examination and imaging, all visible perirectal and involved iliac nodes, including any lymph node in doubt as GTV in the absence of a biopsy.

CTV: CTV should cover the GTV with a 1.5–2-cm margin expansion superiorly and inferiorly but excluding the uninvolved bone, muscle, or air. This volume should include the entire rectum, mesorectum, and the presacral space axially at these levels. A 1–2-cm margin around the gross tumor invasion into the adjacent organs should be added. The coverage of the entire presacral space and mesorectum should be considered. Any mesorectal node visible on CT should be included. Should cover the entire mesorectum and the right and left internal iliac lymph nodes for T3 tumors. The right and left external iliac lymph nodes of T4 tumors with anterior organ involvement should also be included.

To cover the iliac lymphatics, a 0.7-cm margin around the iliac vessels was drawn (excluding the muscle and bone).

To cover the external iliac nodes, an additional 1-cm margin anterolaterally around the vessels was needed. Small adjacent nodes should be included.

Anteriorly, a margin of 1–1.5 cm should be added into bladder to account for changes in bladder and rectal filling. A 1.8-cm-wide volume between the external and internal iliac vessels is needed to cover the obturator nodes

PTV: Each CTV should be expanded by 0.5–1 cm, depending on the physician's comfort level and setup accuracy.

Results

Results Obtained in the Present Study Include

- In the present study, out of the 60 patients with locally advanced rectal cancer, the maximum number of patients was from age group > 60 years.

- Maximum number of cases i.e., 35(58.3%) were males

- Maximum patients were of moderately differentiated adenocarcinoma i.e., 27 (45%)

- Out of 60 patients, maximum number of cases i.e., 27 (45%) were in stage IIIB

- 60 patients were given neoadjuvant chemoradiation with radiation dose of 45Gy/20#/4 weeks and with Capecitabine (825mg/m^2 PO Bid).

- Acute radiation toxicity was assessed using the RTOG criteria. Acute skin toxicity increased significantly from week 1 to after 1 month (overall for all the grades i.e., Total): Chi-square test for linear trend (Extended Mantel Haenszel method), P=0.0001 shown in Table 1. Acute Lower GI toxicity increased significantly from week 1 to after 1 month (overall for all the grades i.e., Total): Chi-square test for linear trend (Extended Mantel Haenszel method), P=0.0001 shown in Table 2. Acute genitourinary toxicity was observed in very few patients i.e., only in 2 (3.3%) patients in week 4 (Only grade1)

- Capecitabine induced toxicity was assessed by CTCAE criteria v5.0, CTCAE criteria Diarrhea toxicity increased significantly from week 1 to after 1 month (overall for all the grades i.e., Total): Chi-square test for linear trend (Extended Mantel Haenszel method), P=0.0001 shown in Table 3. CTCAE criteria Hand Foot Syndrome toxicity increased significantly from week 1 to after 1 month (overall for all the grades i.e., Total): Chi-square test for linear trend (Extended Mantel Haenszel method), P=0.0047, shown in Table 4. Maximum anemia was observed in week 4 (most of the patients had grade 1 anemia. very few grade 2) i.e., in 52 (86.6%) patients. Maximum neutropenia was observed in week 4 (most of the grade 1 only) i.e., in 29 (48.3%) patients. Maximum thrombocytopenia was observed in week 3 (all were grade 1 only) i.e., in 31 (51.6%) patients.

- The radiological (clinical) response was assessed using RECIST 1.1 criteria. Out of 60 patients, it was observed in 59 patients, as 1 patient died after completion of neoadjuvant chemoradiation due to disease related complication. Complete response was observed in 2 patients, partial response in 44, stable disease in 4, and progressive disease in 9 Non- significant trend in radiological response by RECIST category, P=0.1798.

- Of the 50 patients eligible for surgery (excluding those with progressive disease on neoadjuvant chemoradiation), 37 underwent surgery. The remaining 12 patients refused surgery or were lost to follow-up as they did not want a permanent colostomy bag and hence defaulted,1 patient who had complete clinical response following neoadjuvant chemoradiation died due to disease-related complications. Among the 37 patients, 26 underwent abdominoperineal resection (APR) and 11 underwent anterior resection (AR).

- Pathological responses were observed in 37 patients who underwent surgery and were assessed using the Modified Ryan Scheme for Tumor Regression Score (Cap Guideline). Complete response was observed in 1 patient, near- complete response in 7, partial response in 27, and poor or no response in 2 patients. A statistically

Table 1. Distribution of Cases According to RTOG Criteria Acute Skin Toxicity

Grades of Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Duration				
Week 1	0	0	0	0
Week 2	44	0	0	0
Week 3	53	7	0	0
Week 4	22	35	3	0
After 1 month of Completion of RT	33	26	1	0

Table 2. Distribution of Cases According to RTOG Criteria Acute Lower GI toxicity

Grades of Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Duration				
Week 1	1	0	0	0
Week 2	42	1	0	0
Week 3	50	8	1	0
Week 4	24	33	3	0
After 1 month of Completion of RT	47	7	1	0

Table 3. Distribution of Cases According to CTCAE Criteria Diarrhea Toxicity

Grades of Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Duration				
Week 1	0	0	0	0
Week 2	23	1	0	0
Week 3	56	3	1	0
Week 4	29	28	3	0
After 1 month of Completion of RT	33	0	0	0

Table 4. Distribution of Cases According to CTCAE Criteria Hand foot Syndrome Toxicity

Grades of Toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Duration				
Week 1	0	0	0	0
Week 2	0	0	0	0
Week 3	0	0	0	0
Week 4	0	0	0	0
After 1 month of Completion of RT	7	1	0	0

significant trend in pathological response by RYAN score category, P=0.0001.

Discussion

The standard treatment for locally advanced rectal cancer is chemotherapy, followed by total mesorectal excision. Preoperative chemoradiation also significantly decreased the rate of local recurrence compared to postoperative chemo radiation. The present study was conducted in the radiotherapy department of Government Medical College and Cancer Hospital, Aurangabad, Maharashtra, India, which included 60 patients with locally advanced rectal cancer receiving external beam radiation and chemotherapy and assessed the clinical profile and toxicity of patients treated with neoadjuvant chemoradiotherapy.

In the present study, a maximum patients i.e., 17 patients were in the age group > 60 years (Table 5), maximum patients was 35 males, that is, 22 patients had weights in the range of 41 to 50 kg.

In Previous study by JUN-SANG KIM et al (2002) [15]. In this study, between July 1999 and March 2001, 45 patients with locally advanced rectal cancer with age from 36- 80 with median age 62 (58% male and 48% female) were treated with pre-operative chemoradiation. Juergen Dunst et al (2008) [16] 96 patients age 34 to 81 yrs. (63% male and 37% female) with median age 65 from seven German university centers entered the study between June 2001 and November 2003. A De Paoli et al (2006) [17] A total of 53 patients were recruited for the study between September 2001 and July 2003. The median age of the patients was 63 years (range, 29–80 years).

In the present study, 51 patients had CEA level of >5ng/ml. In the maximum cases, that is, 27, moderately differentiated adenocarcinoma was found. Stage III B disease was found in the maximum number of patients (27).

In a Previous study by Jun-Sang Kim et al (2002) [15] 45 patients with locally advanced rectal cancer (cT3/T4 or N+) were treated with preoperative chemoradiation. A radiation dose of 45 Gy/25 fractions was delivered to the pelvis, followed by a dose of 5.4 Gy/3 fractions boosted to the primary tumor. Chemotherapy was administered concurrently with radiotherapy and consisted of two cycles of 14-day oral capecitabine (1650 mg/m^2 /day) and leucovorin (20 mg/m^2 /day), each of which was followed by a 7-day rest period. Surgery was performed 6 weeks after the completion of chemoradiation. Juergen Dunst et al (2008) [16] Most of the patients who had a locally advanced primary tumor (cT3:57%, cT4: 40%) had lymph node involvement in 60%. All received a total radiation dose of 50.4–55.8 Gy with conventional fractions. Capecitabine was administered at an oral dosage of 825 mg/m^2 bid on each day of the radiotherapy period, with the first daily dose applied 2h before irradiation,

Table 5. Patient and Tumor Characteristics

Characterstics	Number (%)
Age (Years)	21-85 (52)
Sex	
Male	35 (58)
Female	25 (42)
ECOG Performance Status	
0	2 (3)
1	56 (94)
2	2 (3)
Pathological Differentiation	
Well-Differentiated Adenocarcinoma	18 (30)
Moderately-Differentiated Adenocarcinoma	25 (42)
Poorly-Differentiated Adenocarcinoma	11 (18)
Others (Mucinous, Signet Ring)	6 (10)
TNM Staging	
T2N1	12 (20)
T2N2	14 (23)
T3N0	05 (08)
T3N1	09 (15)
T3N2	19 (32)
T4N1	00 (00)
T4N2	01 (02)
Group Stage	
IIA	5 (08)
IIB	0 (00)
IIC	0 (00)
IIIA	13 (20)
IIIB	27 (45)
IIIC	15 (27)

followed by surgery 6 weeks later. De Paoli et al (2006) [17]. A total of Fifty-three patients were recruited for the study between September 2001 and July 2003. The median age was 63 years (range 29–80), and the majority of patients (87%) had T3, N0–2, M0 stage of disease and were treated with capecitabine (825 mg/m^2, twice daily, 7 days per week) and concomitant RT (50.4Gy/28 fractions).

A total of 59 out of 60 patients who underwent CT scan 6 weeks after completion of neoadjuvant chemoradiation, radiological response (Clinical response) according to Recist 1.1 CRITERIA complete response was observed in 2 patients, partial response in 44 patients, stable disease in 4 patients, and progressive disease in 9 patients' non-significant trend in radiological response was seen according to Recist 1.1 criteria, P=0.1798, which is approaching to significant value.

Fifty patients were eligible for surgery among the 60 study subjects, of which 37 underwent surgery. The remaining 13 patients refused surgery or were lost to follow-up. Of the 37 patients, 26 patients have undergone abdominoperineal resection (APR) and 11 underwent anterior resection (AR) surgery.

Pathological response was observed according to Modified Ryan scheme for Tumor Regression score (CAP guidelines), complete response was observed in 1 patient, near complete response in 7 patients, partial response in 27 patients, and poor or no disease in 2 patients; a statistically significant trend in pathological response was seen by the Modified Ryan scheme for tumor regression score (CAP guidelines) score (P=0.0001, which is significant.)

In a previous study by JUN-SANG KIM et al (2002) [15] Thirty-eight patients received definitive surgery. Primary tumor and node downstaging observed in 63% and 90% of patients, respectively. The overall downstaging rate, including both the primary tumors and nodes, was 84 percent. A pathologic complete response was observed in 31% of patients. 21 patients had tumors situated initially 5 cm or less from the anal verge; among the 18 treated with surgery, 72% underwent sphincter-preserving surgery. Grade 2 leukopenia and anemia developed in 7% and 9% of patients, respectively. Grade 3 non-hematologic toxicities that developed included hand foot syndrome in 7%), fatigue in 4%), diarrhea in 4%), and radiation dermatitis in 2% of patients.

Juergen Dunst et al (2008) [16] Most of the patients suffered from an advanced primary tumor (cT3: 57%, cT4: 40%) with lymph node involvement in sixty percent. After preoperative treatment, with a mean of 99% of the radiation dose actually delivered, a clinical response rate of 68% (95% confidence interval: 57–78%) was observed. Out of 87 patients undergoing surgery, a sphincter-preserving surgery could be done in 51% and R0 resection in 94%.A pathologically complete response was observed in 6 patients (7%, 95% confidence interval: 3–14%). By comparing the initial diagnosis and pathologic findings showed a downstaging in Sixty one percent. Acute toxicity with greater than five percent incidence of NCI (National Cancer Institute) grade ≥ 3 included lymphopenia (12%), leukopenia (6%), and diarrhea (7%). Mild to moderate hand-foot syndrome seen in 12% only.

A De Paoli et al (2006) [17]: All patients but two completed the RT program and 47 (89%) received 81%–100% of the capecitabine dose (100% of dose in 72% patients, 81%–95% in 17% patients, and 48%–74% in 11% of patients). Grade 3 toxicity occurred in six patients (11%), included mainly of leukopenia (4%) and hand–foot syndrome (4%). Mild to moderate toxicity was observed, including leukopenia (72%), diarrhea (40%), proctitis (34%), and skin toxicity (20%). The overall clinical response rate was fifty eight percent, the downstaging rate was fifty seven percent the a pathologic complete response rate was 24%. Among 34 patients with low-lying tumors (5 cm from anal verge), 20 (59%) underwent a sphincter-saving operation.

The response to preoperative CT–RT has been reported to possibly increase the feasibility of sphincter-preserving surgery and, potentially, to impact disease control and survival. Newer strategies in preoperative treatment of rectal cancer have been directed to obtain higher complete response rates. The combination of 5-FU with new effective drugs for colorectal cancer, such as oxaliplatin and irinotecan, has demonstrated a significant increase in

response to advanced disease.

In this study, we used capecitabine, which is an active and safe oral fluoropyrimidine in combination with RT, as demonstrated in our study, which might simplify chemoradiation by replacing ci-5-FU and the necessity of central lines in these newer preoperative approaches.

In conclusion, preoperative chemoradiation has become a part of treatment protocols for locally advanced rectal cancer. Preoperative chemoradiation can lead to tumor downstaging and improved resectability in locally advanced rectal cancer. It also permits sphincter preservation in distal rectal cancer and has a positive impact on the quality of life. The present study was conducted among histologically proven locally advanced rectal adenocarcinoma patients who received neoadjuvant chemoradiation with capecitabine (825mg/m^2 PO bid) with radiation (45 Gy/20 #/4weeks). From this study, we concluded that preoperative chemoradiation with capecitabine is a safe, well-tolerated, and effective neoadjuvant treatment modality for locally advanced rectal cancer and has a considerable downstaging effect on the tumor.

Conflict of Interest

We declare no Conflict of Interest

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